PA NT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 October 2000 (03.10.00)	
International application No. PCT/GB00/00481	**Applicant's or agent's file reference** PHM70481/WO
International filing date (day/month/year) 15 February 2000 (15.02.00)	**Priority date** (day/month/year) 17 February 1999 (17.02.99)
Applicant KOIKE, Haruo et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 August 2000 (30.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

BRYANT, Tracey
Global Intellectual Property,
Patents.
AstraZeneca UK Limited
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
ROYAUME-UNI

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 11 August 2000 (11.08.00)	
Applicant's or agent's file reference PHM70481/WO	IMPORTANT NOTIFICATION
International application No. PCT/GB00/00481	International filing date (day/month/year) 15 February 2000 (15.02.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ASTRAZENECA UK LIMITED 15 Stanhope Gate London W1Y 6LN United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
ASTRAZENECA AB S-151 85 Södertälje Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The person appearing in Box 1 above has assigned all rights to the person appearing in Box 2.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer R. Chrem
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

BRYANT, Tracey
Global Intellectual Property,
Patents.
AstraZeneca UK Limited
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
ROYAUME-UNI

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 04 May 2000 (04.05.00)	
Applicant's or agent's file reference PHM70481/WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/00481	**International filing date** (day/month/year) 15 February 2000 (15.02.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address

ZENECA LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address

ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Lazar Joseph Panakal
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PHM70481/WO

Box No. I TITLE OF INVENTION

CHEMICAL PROCESS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ZENECA Limited
15 Stanhope Gate,
London. W1Y 6LN.
GB

☐ This person is also inventor.

Telephone No.
(01625) 516173

Facsimile No.
(01625) 583358

Teleprinter No.

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SHIONOGI & CO LTD.
1-8 Doshomachi
3-Chome, Chuo-ku
Osaka 541-0045
JP

This person is:

☒ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is,country)* of nationality: JP

State *(that is, country)* of residence: JP

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BRYANT, Tracey
Global Intellectual Property, Patents.
AstraZeneca UK Limited
Mereside, Alderley Park,
Macclesfield, Cheshire. SK10 4TG
GB

Telephone No.
(01625) 513228

Facsimile No.
(01625) 583358

Teleprinter No.

☐ **Adress for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KOIKE, Haruo
1-3 Kuise Terajima 2-Chome
Amagasaki-shi
Hyogo 660-0813
JP

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: JP

State *(that is, country)* of residence: JP

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KABAKI, Mikio
1-3 Kuise Terajima 2-Chome
Amagasaki-shi
Hyogo 660-0813
JP

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: JP

State *(that is, country)* of residence: JP

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TAYLOR, Nigel Philip
Mereside, Alderley Park,
Macclesfield,
Cheshire. SK10 4TG.
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DIORAZIO, Louis Joseph
Mereside, Alderley Park,
Macclesfield,
Cheshire. SK10 4TG.
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] AP **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] EA **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] EP **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] OA **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] AL Albania .....
- [X] AM Armenia .....
- [X] AT Austria .....
- [X] AU Australia .....
- [X] AZ Azerbaijan
- [X] BA Bosnia and Herzegovina .....
- [X] BB Barbados
- [X] BG Bulgaria .....
- [X] BR Brazil .....
- [X] BY Belarus .....
- [X] CA Canada
- [X] CH and LI Switzerland and Liechtenstein
- [X] CN China .....
- [X] CU Cuba .....
- [X] CZ Czech Republic .....
- [X] DE Germany .....
- [X] DK Denmark .....
- [X] EE Estonia .....
- [X] ES Spain .....
- [X] FI Finland .....
- [X] GB United Kingdom
- [X] GE Georgia .....
- [X] GH Ghana .....
- [X] GM Gambia
- [X] GW Guinea-Bissau .....
- [X] HR Croatia
- [X] HU Hungary .....
- [X] ID Indonesia
- [X] IL Israel .....
- [X] IS Iceland
- [X] JP Japan .....
- [X] KE Kenya .....
- [X] KG Kyrgyzstan .....
- [X] KP Democratic People's Republic of Korea .....
- [X] KR Republic of Korea .....
- [X] KZ Kazakhstan .....
- [X] LC Saint Lucia
- [X] LK Sri Lanka
- [X] LR Liberia
- [X] LS Lesotho .....
- [X] LT Lithuania
- [X] LU Luxembourg
- [X] LV Latvia
- [X] MD Republic of Moldova .....
- [X] MG Madagascar .....
- [X] MK The former Yugoslav Republic of Macedonia .....
- [X] MN Mongolia
- [X] MW Malawi .....
- [X] MX Mexico .....
- [X] NO Norway
- [X] NZ New Zealand .....
- [X] PL Poland .....
- [X] PT Portugal .....
- [X] RO Romania
- [X] RU Russian Federation .....
- [X] SD Sudan
- [X] SE Sweden
- [X] SG Singapore
- [X] SI Slovenia .....
- [X] SK Slovakia .....
- [X] SL Sierra Leone
- [X] TJ Tajikistan .....
- [X] TM Turkmenistan .....
- [X] TR Turkey .....
- [X] TT Trinidad and Tobago .....
- [X] UA Ukraine .....
- [X] UG Uganda .....
- [X] US United States of America .....
- [X] UZ Uzbekistan .....
- [X] VN Viet Nam .....
- [X] YU Yugoslavia .....
- [X] ZW Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- [X] .....
- [X] .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental B x *If the Supplemental Box is not used, this sheet should not be included in the request.*

*1. If, in any of the Boxes, **the space is insufficient** to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

*(i) **if more than two persons are involved as applicants and/or inventors** and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

*(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication **"the States indicated in the Supplemental Box"** is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

*(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America**: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

*(iv) if, in addition to the agent(s) indicated in Box No. IV, there are **further agents**: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

*(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "**patent of addition**," or "**certificate of addition**," or if, in Box No. V, the name of the United States of America is accompanied by an indication "**continuation**" or "**continuation-in-part**": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

*(vi) if, in Box No. VI, there are **more than three earlier applications whose priority is claimed**: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*

*(vii) if, in Box No. VI, **the earlier application is an ARIPO application**: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.*

*2. If, with regard to the **precautionary designation statement** contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

*3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning **non-prejudicial disclosures or exceptions to lack of novelty**: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

Box No. VI PRIORITY CLAIM ☐ Further priority claim is indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 17 FEB 1999 (17/02/99)	9903472.0	GB		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 04
description (excluding sequence listing part)	: 10
claims	: 03
abstract	: 01
drawings	:
sequence listing part of description	:
Total number of sheets	: 18

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

BRYANT, Tracey
Agent for Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Artic 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PHM70481/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 00481	15/02/2000	17/02/1999
Applicant		
ZENECA LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   PROCESS FOR THE PRODUCTION OF TERT-BUTYL (E)-(6-[2-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL(METHYLSULFONYL)AMINO]PYRIMIDIN-5-YL]VINYL](4R,6S)-2,2-DIMETHYL[1,3]DIOXAN-4-YL)ACETATE

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with th abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/00481

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	G. WESS ET AL.: "Stereoselective synthesis of HR 780, a new highly potent HMG-CoA reductase inhibitor" TETRAHEDRON LETTERS, vol. 31, no. 18, 1990, pages 2545-2548, XP002010060 * Scheme 2 * ---	1-10
Y	T. MINAMI, T. HIYAMA: "A novel enantioselective synthesis of HMG Co-A reductase inhibitor NK-104 and a related compound" TETRAHEDRON LETTERS, vol. 33, no. 49, 1992, pages 7525-7526, XP000886341 * Scheme 1 * --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 2000	17/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PHM70481/EPT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00481	15/02/2000	17/02/1999
International Patent Classification (IPC) or national classification and IPC C07D405/06		
Applicant ASTRAZENECA AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/08/2000	15.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herz, C Telephone No. +49 89 2399 8275

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00481

I. Basis f the r p rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-10 as originally filed

Claims, No.:

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations
see separate sheet

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	T. MINAMI ET AL.: "Stereoselctive reducton of beta, delta-diketo esters derived from tartaric acid. A facile route to optically active 6-oxo-3,5-syn-isopropylidenedioxyhexanoate , a versatile synthetic intermediate of artificial HMG Co-A reductase inhibitors" TETRAHEDRON LETTERS, vol. 34, no. 3, 1993, pages 513-516, XP000886348 page 516 ---	1-10
Y	T. HIYAMA ET AL.: "Synthesis of Artificial HMG-CoA Reductase Inhibitors Based on the Olefination Strategy" BULL. CHEM. SOC. JPN., vol. 68, no. 1, 1995, pages 364-372, XP000886402 * Scheme 3 * table 1 ---	1-10
Y	WO 97 19917 A (L'OREAL) 5 June 1997 (1997-06-05) claim 47 -----	1-10

INTERNATIONAL SEARCH REPORT

Information [redacted] patent family members

International Application No
PCT[redacted] 00/00481

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719917 A	05-06-1997	FR 2741620 A	30-05-1997
		EP 0805800 A	12-11-1997
		JP 10504845 T	12-05-1998

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Published
With international search report.

(54) Title: PROCESS FOR THE PRODUCTION OF TERT–BUTYL (E)–(6–[2– [4–(4–FLUOROPHENYL) –6–ISOPROPYL–2–[METHYL (METHYLSULFONYL) AMINO] PYRIMIDIN–5–YL] VINYL](4R, 6S)–2,2–DIMETHYL [1,3]DIOXAN–4–YL) ACETATE

(57) Abstract

The invention concerns a process for the manufacture of tert–butyl (E)–(6–[2– 4–(4–fluorophenyl) –6–isopropyl–2–[methyl (met hylsulfonyl) amino] pyrimidin–5–yl] vinyl}–(4R, 6S)–2,2–dimethyl [1,3–dioxan–4–yl) acetate, the novel starting material used in said process and the use of the process in the manufacture of a pharmaceutical.

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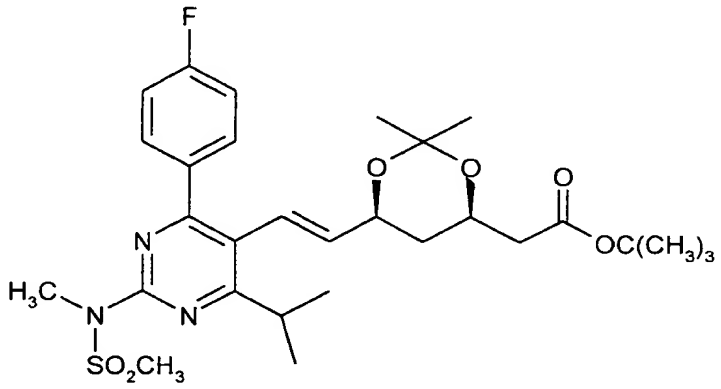
PROCESS FOR THE PRODUCTION OF TERT-BUTYL (E)-(6-[2-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL(METHYLSULFONYL)AMINO]PYRIMIDIN-5-YL]VINYL](4R,6S)-2,2-DIMETHYL[1,3]DIOXAN-4-YL)ACETATE

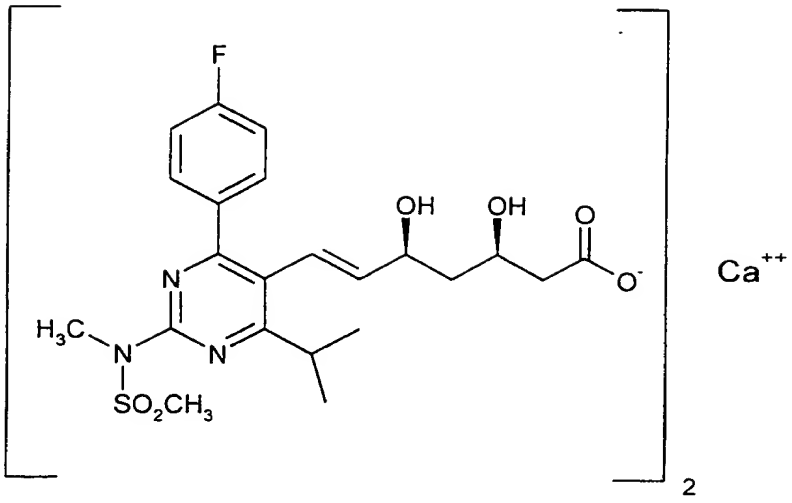
This invention concerns a novel chemical process, and more particularly it concerns a novel chemical process for the manufacture of tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate of formula I,



Formula I

(hereinafter referred to as BEM) which is useful, for example, as a chemical intermediate in the production of a pharmaceutical useful in the treatment of, inter alia, hypercholesterolemia, hyperlipoproteinemia and atherosclerosis. The invention further includes the novel starting material used in said process and the use of the process in the manufacture of an HMG CoA reductase inhibitor.

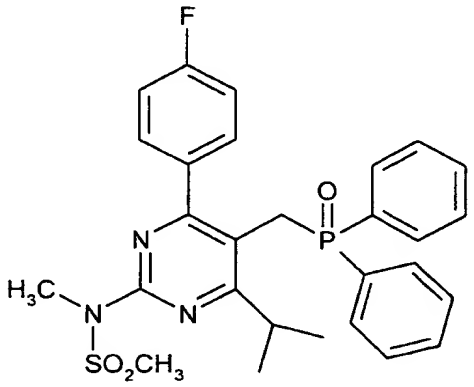
In European Patent Application, Publication No. (EPA) 0521471 is disclosed (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid and its sodium salt and calcium salt (illustrated below)



(hereinafter referred to collectively as "The Agent") as inhibitors of HMG CoA reductase. The Agent is obtained therein via reduction of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonyl-amino)pyrimidin-5-yl-(3R)-3-hydroxy-5-oxo-(E)-heptenoate and subsequent processing. However the Agent may be obtained from BEM by treatment with acid (to cleave the acetonide protecting group) followed by base (to cleave the ester) and (as described in EPA 0521471) conversion of the initially formed salt to the free acid or the calcium salt.

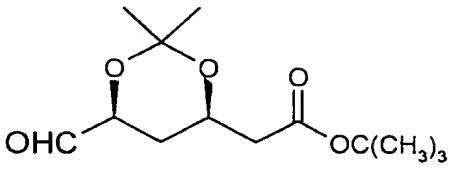
We have now discovered a useful and advantageous process for preparing BEM.

According to the invention there is provided a process for preparing BEM (formula I) which comprises reaction of diphenyl [4-(4-fluoropheny)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl] phosphine oxide of formula III



Formula III

(hereinafter referred to as DPPO) with tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl}acetate of formula II



Formula II

(hereinafter referred to as BFA) in the presence of a strong base.

The process is carried out in a suitable solvent, or mixture of solvents for example, ethereal or aromatic solvents or mixtures thereof. Particularly suitable solvents include, for example, tetrahydrofuran (THF), dimethoxyethane and toluene, or mixtures thereof. Particularly preferred solvents include, for example, THF and THF and toluene.

Suitable bases for use in the process include, for example, amide bases, alkyl metals and metal hydrides. Particular bases include, for example, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium bis(trimethysilyl)amide, butyllithium and sodium hydride. A particularly preferred base is, for example, sodium bis(trimethylsilyl)amide (NaHMDS).

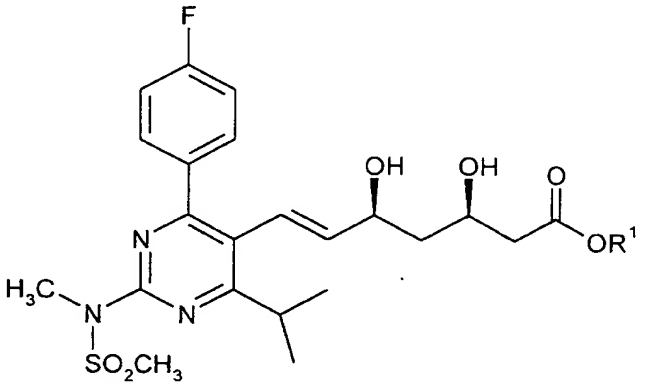
The reaction may be carried out at a temperature in the range of, for example, -20°C to -90°C, such as -40°C to -90°C, for example -40°C to -80°C. A convenient temperature at which to carry out the reaction is, for example, that of a mixture of acetone and solid carbon dioxide (about -75°C).

The process is advantageously carried out with 1.0 to 1.2 equivalents of base (per equivalent of DPPO), such as 1.05 to 1.2 equivalents and preferably 1.05 to 1.12 equivalents. Although BFA can be present in large excess, it is convenient to use 1.0 to 1.35 equivalents (per equivalent of DPPO), and preferably 1.05 to 1.3 equivalents, especially 1.05 to 1.15 equivalents.

The process of the invention provides significantly improved yields and quality of product by comparison to when a corresponding dialkyl phosphonate (-PO(Oalkyl)$_2$) starting material is used instead of DPPO.

The starting material, DPPO, which is a further aspect of the present invention, may be obtained as described in the Examples hereinafter, starting from an alkyl 2-amino-4-(4-fluorophenyl)-6-isopropylpyrimidin-5-carboxylate, for example the methyl ester which may be obtained as described in Japanese Patent Application No. 06-256318, or the ethyl ester which may be obtained as described in EPA 0521471. BFA may be obtained as described in EPA 0319847 (Example 6).

A further aspect of the present invention is a process for the manufacture of a compound of the formula IV



Formula IV

in which R^1 is hydrogen or a pharmaceutically acceptable cation, which comprises;

(1) reaction of DPPO with BFA in the presence of a strong base (as described above) to give BEM;

(2) cleavage of the dihydroxy (acetonide) protecting group (for example by acid hydrolysis, such as by using HCl in THF or acetonitrile); and

(3) cleavage of the tert-butyl ester group under basic conditions to form a compound of the formula IV in which R^1 is a pharmaceutically acceptable cation (for example by using a solution of a metallic hydroxide in a polar solvent, such as using aqueous sodium hydroxide in ethanol or acetonitrile to form the sodium salt);

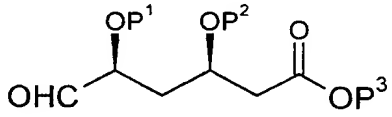
optionally followed by neutralisation to give a compound of the formula IV in which R^1 is hydrogen;

and/or optionally followed by conversion to another compound of the formula IV in which R^1 is a pharmaceutically acceptable cation (for example conversion of the sodium salt to the

calcium salt by treatment with a water soluble calcium salt (such as calcium chloride) under aqueous conditions).

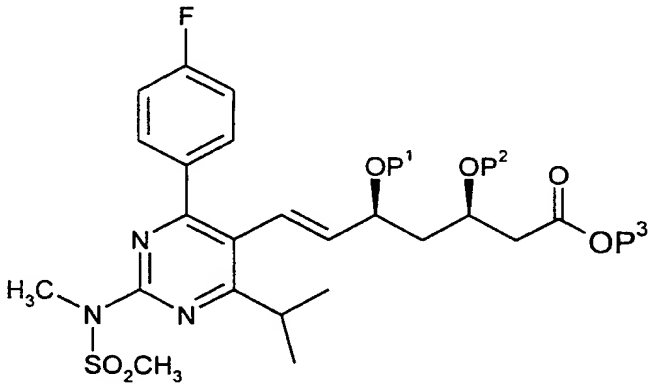
Suitable conditions for steps (2), (3) and the subsequent optional steps are analogous to, or the same as, those disclosed in EPA 0521471 and/or EPA 0319847, which are hereby incorporated herein by reference. To obtain the calcium salt of the compound of formula IV, as illustrated on page 1, preferably steps (2), (3) and conversion to the calcium salt via the methylamine salt are carried out as described in Example 7, which steps form a further aspect of the invention.

It will be appreciated that, in the processes described above, BFA may be replaced by a compound of the general formula V



Formula V

in which P^1 and P^2 are alcohol protecting groups, or P^1 and P^2 taken together is a 1,3-diol protecting group, such as those described in EPA 0319847 and GB 2244705 which are included herein by reference, and P^3 is a carboxylic acid protecting group, for example (1-8C)alkyl (such as (1-4C)alkyl), to form a compound of the formula VI



Formula VI

The compound of the formula VI may be converted to the Agent by cleavage of the alcohol or diol protecting groups and conversion of the $COOP^3$ to a COOH group or a pharmaceutically acceptable salt thereof. Such general processes form further features of the present invention.

The invention is further illustrated, but not limited by the following Examples.

Preparation 1

Preparation of DPPO

A stirred mixture of methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-carboxylate (12.0 g) in toluene (55ml) was cooled to -10°C and diisobutyl aluminium hydride (50 ml of a 1.5M solution in toluene) was added over two hours maintaining the temperature below 0°C. After addition, the mixture was stirred for 30 minutes at 0°C. Methanol (0.64 ml) was added to the mixture maintaining the temperature at 0°C. The mixture was then added over two hours to a stirred mixture of concentrated hydrochloric acid (23.3 ml), water (40.5 ml) and acetonitrile (24 ml) at 40°C, maintaining the temperature of the mixture at 40°C. After addition, the mixture was stirred at 40°C for a further 30 minutes and then purged with nitrogen (to remove any isobutane). The mixture was cooled to 20°C and allowed to stand for 20 minutes. The organic phase was separated and washed with a mixture of concentrated hydrochloric acid (0.7 ml) and water (30 ml). Acetonitrile (24 ml) was added to the organic phase and the mixture washed with a solution of sodium bicarbonate (0.038 g) in water (120 ml).

The organic phase was heated to 40°C, and then from 40°C to 80°C using a nitrogen purge. The mixture was concentrated by distillation at atmospheric pressure, collecting 54 ml of distillate. Acetonitrile (24 ml) was added to the concentrated solution and phosphorus tribromide (1.2 ml) was added with stirring, maintaining the temperature of the mixture at 20°C. After addition, the mixture was stirred at 20°C for 30 minutes. The mixture was added to water (36 ml) over 30 minutes maintaining the temperature at 20°C. The mixture was stirred for 5 minutes and the organic phase separated. The organic phase was washed with a solution of sodium bicarbonate (0.027 g) in water (36 ml), followed by water (36 ml). The organic phase was distilled under reduced pressure until 29 ml of distillates was collected. The mixture was cooled to 60°C and ethyl diphenylphosphinite (7.47 ml) was added. The mixture was stirred at 60°C for 3 hours, then heated to reflux. Toluene (40 ml) was added and the mixture cooled to 0°C over 2 hours. The product was collected by filtration, washed with cold toluene (10 ml) and dried under vacuum at 50°C to give DPPO (14.66 g); ^{1}HNMR ($CDCl_3$, 270 MHz): 7.42 [m, 10H, $P(C_6\underline{H}_5)_2$], 7.12 [m, 2H, Ar-H], 6.92 [m, 2H, Ar-H], 3.92 [d,2H, $C\underline{H}_2P$], 3.51, 3.46 (2 x s, 6H, $NC\underline{H}_3$ $SO_2C\underline{H}_3$], 3.43 [hept., 1H, $C\underline{H}(CH_3)_2$], 1.25 [d, 6H, $CH(C\underline{H}_3)_2$]

Methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino)pyrimidine-5-carboxylate was prepared as follows:

A mixture of methyl 2-amino-4-(4-fluorophenyl)-6-isopropyl-pyrimidine-5-carboxylate (19.0 g), sodium tert-pentoxide (22.95 g) and dimethoxyethane (190 ml) was stirred for 30 minutes at 25°C. The stirred mixture was cooled to -10°C and methanesulfonyl chloride (8.4 ml) was added dropwise, maintaining the temperature of the mixture at -5°C. After 20 minutes, dimethyl sulfate (8.1 ml) was added and the mixture allowed to warm to 25°C. The mixture was stirred for one hour at 25°C and a solution of sodium tert-pentoxide (1.91 g) in dimethoxyethane (10 ml) added. The mixture was stirred for one hour at 25°C. A solution of sodium chloride (13.3 g) in water (133 ml) was added and the mixture was stirred for 10 minutes at 25°C. The mixture was allowed to settle for 15 minutes and the lower aqueous phase was separated and discarded. Water (38 ml) was added to the remaining mixture and the mixture was stirred for 30 minutes at 25°C. The mixture was then heated to obtain a complete solution. The mixture was cooled slowly to 25°C over one hour. The mixture was cooled to 0°C, stirred for one hour, and the suspended solid collected by filtration. The solid was washed with cold (0°C) solution of 50:50 water/dimethoxyethane (20 ml). The solid was dried under vacuum at 60°C to give methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-carboxylate (19.35 g); ^{1}HNMR (270 MHz, $CDCl_3$): 7.69 (m,2H), 7.14 (m,2H), 3.71, 3.60, 3.51 (3 x s, 9H), 3.20 (m, 1H), 1.32 (d,6H).

Example 1

A mixture of DPPO (19.17 g) and THF (227 ml) were warmed briefly to 40°C until a clear solution had formed then inerted by the sequential application of vacuum and nitrogen (5 cycles). The mixture was immersed in an acetone/CO_2 bath cooling the contents to -75°C. Sodium bis(trimethylsilyl)amide (37.4 ml of 1.0M solution in THF) was added to the reaction mixture over 10 minutes from a pressure equalising dropping funnel maintaining the temperature below -74°C and forming a red solution of the anion. THF (10 ml) was rinsed through the dropping funnel into the mixture and the mixture stirred a further 1 hour at -76°C forming a red suspension. BFA (80 ml of ~13.5% w/w toluene solution) was added in portions to the suspension over 20 minutes from a pressure equalising dropping funnel maintaining the temperature below -73°C. Toluene (20 ml) was rinsed through the dropping

funnel into the mixture and the mixture stirred a further 15 minutes at -76°C. The chilling bath was lowered and the suspension allowed to warm to 10°C over 1.5 hours. Glacial acetic acid (3.21 g) in water (15 g) was added in one portion raising the temperature to 18°C and dissolving all solids and the mixture was stirred a further 5 minutes.

The mixture was concentrated by distillation at atmospheric pressure (jacket 110°C) to a temperature of 94°C collecting a total of 274 ml distillates. The concentrated mixture was cooled to 40°C, water (40 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded. Sodium hydrogen carbonate (2.99 g) in water (40 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded. Water (30 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded.

The organic phase was transferred to a distillation apparatus with toluene (20 ml) and concentrated by distillation at atmospheric pressure (jacket 125-130°C) to a temperature of 116°C collecting 85 ml distillates. Vacuum was applied (400-500 mbar) and a further 16.5 ml distillates collected to a temperature of 111°C. The vacuum was released and the concentrated mixture allowed to cool to 80°C. Warm MeOH (140 ml, 50°C) was added with rapid stirring and the batch allowed to self-cool to 20°C over 30 minutes during which time a solid was deposited. The suspension was further cooled to 2°C for 30 minutes then the solid was collected by filtration on a sinter and pulled as dry as possible. The solid was washed with cold MeOH (60 ml, 2°C) and again pulled as dry as possible then transferred to a vacuum oven and dried overnight (50°C, 200 mbar); giving BEM (14.01 g, 67.7%).

^{1}H NMR ($CDCl_3$, 270 MHz)

7.65 [m, 2H, Ar-H], 7.09 [m, 2H, Ar-H], 6.52 [dd, 1H, ArCH=CH], 5.47 [dd, 1H, ArCH=CH], 3.57, 3.50 [2 x s, 6H, NCH_3, SO_2CH_3], 3.38 [hept., 1H, Ar-$CHMe_2$], 2.45, 2.30 [2 x dd, 2H, CH_2CO_2tBu], 1.55, 1.13 [dt, dd, 2H, acetonide CH_2], 1.50, 1.40 [2 x s, 6H, acetonide $C(CH_3)_2$], 1.45 [s, 9H, $CO_2C(CH_3)_3$], 1.27 [dd, 6H, $ArCH(CH_3)_2$]

Examples 2-6

The procedure as described in Example 1 was carried out using the ratios of reactants and the temperatures given in Table 1. There was thus obtained BEM in the yields given.

Table 1

Wt DPPO	Temp. (°C)	Eq. NaHMDS	Eq. BFA	BEM Yield
10.00 g	-75	1.12	1.20	69.2%
18.12 g	-75	1.12	1.20	69.6%
12.08 g	-75	1.06	1.26	72.8%
19.17 g	-40	1.05	1.06	56.7%
9.57 g	-90	1.05	1.10	72.0%
9.57 g	-60	1.05	1.10	70.1%

Example 7

A mixture of BEM (5.0 g) and acetonitrile (35 ml) was stirred under an inert atmosphere at 40°C. 0.02M hydrochloric acid (9.5 ml) was added over 30 minutes to the resultant solution, maintaining the temperature at 35°C to 42°C. The mixture was stirred at 40°C for 3 hours then cooled to 25°C. 1.0M sodium hydroxide solution (9.5 ml) was added with stirring at 25°C and the mixture was stirred for an additional one hour at 25°C. Sodium chloride (4.7 g) was added and the mixture was cooled to -5°C over one hour. Sufficient of a solution of 1M hydrochloric acid (9.5 ml) and sodium chloride (2.4 g) was added at -5°C to achieve a pH of 3.4 to 4.0 and the mixture stirred at this temperature for 5 minutes. The mixture was allowed to settle for 10 minutes at -5°C to give two layers. The lower layer was separated and discarded. Acetonitrile (65 ml) at -5°C was added to the remaining solution and the mixture was filtered through a filter agent. 40% methylamine solution in water (1.1 ml) was added at -5°C and the mixture was warmed to 30°C over 40 minutes and maintained at this temperature for 90 minutes. The mixture was then cooled to 0°C over 40 minutes and maintained at this temperature for 90 minutes. The resultant solid was collected by filtration and washed with acetonitrile (2x12 ml). The solid, which is the methylamine salt of the compound of formula IV ($R^1 = MeNH_3^+$), was dried under vacuum at 35°C (3.87 g). 8% w/w aqueous sodium hydroxide (5.44 ml) was added to a stirred mixture of the methylamine salt (6.0 g) in degassed water (30 ml) at 20°C and the mixture was stirred for one hour. The mixture was filtered and concentrated under reduced pressure at 40°C until 24 ml of distillate collected. Water (24 ml) was added and the mixture again concentrated under reduced

pressure at 40°C until 24 ml of distillate collected. Water (30 ml) was added and a solution of calcium chloride dihydrate (1.03 g) in water (6 ml) was added dropwise at 20°C. The mixture was stirred for 45 minutes and the resultant solid filtered. The solid was washed with water (36 ml) and dried under vacuum at 40°C to give the calcium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid.

Claims

1. A process for the manufacture of tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}-(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate which comprises reaction of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide with tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate in the presence of a strong base.

2. A process as claimed in claim 1 wherein the reaction is carried out at a temperature in the range of -20°C to -90°C.

3. A process as claimed in claim 1 or 2 wherein the strong base is sodium bis(trimethylsilyl)amide.

4. A process as claimed in claim 1, 2 or 3 wherein the reaction is carried out in a solvent selected from tetrahydrofuran, dimethoxyethane and toluene, and mixtures thereof.

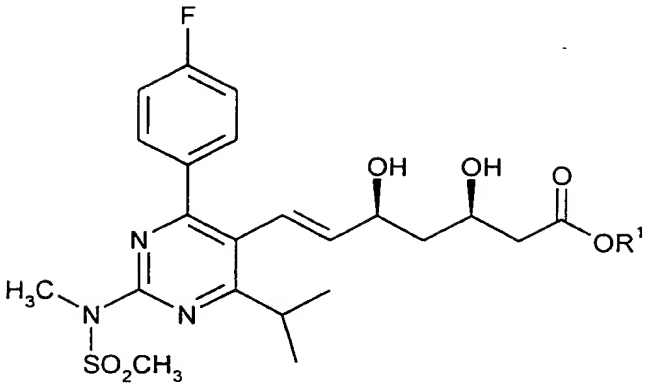
5. A process as claimed in any of claims 1 to 4 wherein 1.0 to 1.2 equivalents of base are used per equivalent of the phosphine oxide.

6. A process as claimed in any of claims 1 to 5 wherein 1.0 to 1.35 equivalents of tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate are used per equivalent of the phosphine oxide.

7. The compound diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide.

8. The compound tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}-(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate.

9. A process for the manufacture of a compound of the formula IV



Formula IV

in which R^1 is hydrogen or a pharmaceutically acceptable cation which comprises

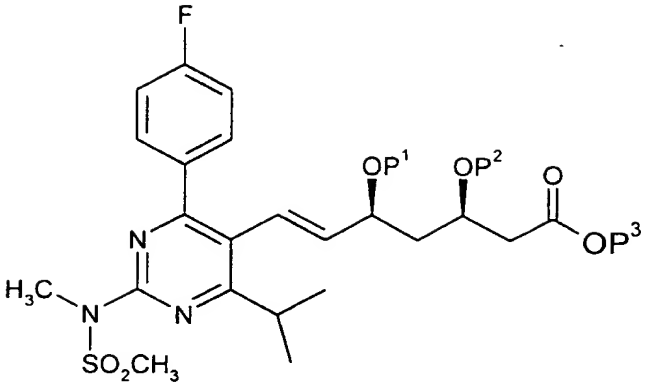
(1) reaction of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide with tert-butyl 2-[(4R, 6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate in the presence of a strong base to give tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]-pyrimidin-5-yl]vinyl}(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate of formula I;

(2) cleavage of the dihydroxy protecting group from the product of step (1);

(3) cleavage of the tert-butyl ester group under basic conditions from the product of step (2) to form a compound of the formula IV in which R^1 is a pharmaceutically acceptable cation;

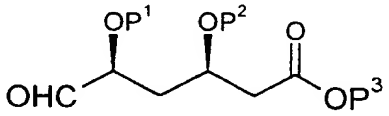
optionally followed by neutralisation to give a compound of the formula IV in which R^1 is hydrogen; and/or optionally followed by conversion to another compound of the formula IV in which R^1 is a pharmaceutically acceptable cation.

10. A process for the manufacture of a compound of the formula VI



Formula VI

which comprises reaction of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide with a compound of the formula V



Formula V

in the presence of a strong base, wherein P^1 and P^2 are alcohol protecting groups, or P^1 and P^2 taken together is a 1,3-diol protecting group, and P^3 is a carboxylic acid protecting group.

INTERNATIONAL SEARCH REPORT

Interr. ıal Application No
PCT/GB 00/00481

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	G. WESS ET AL.: "Stereoselective synthesis of HR 780, a new highly potent HMG-CoA reductase inhibitor" TETRAHEDRON LETTERS, vol. 31, no. 18, 1990, pages 2545-2548, XP002010060 * Scheme 2 *	1-10
Y	T. MINAMI, T. HIYAMA: "A novel enantioselective synthesis of HMG Co-A reductase inhibitor NK-104 and a related compound" TETRAHEDRON LETTERS, vol. 33, no. 49, 1992, pages 7525-7526, XP000886341 * Scheme 1 *	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 April 2000	17/05/2000

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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 00/00481

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	T. MINAMI ET AL.: "Stereoselctive reducton of beta, delta-diketo esters derived from tartaric acid. A facile route to optically active 6-oxo-3,5-syn-isopropylidenedioxyhexanoate , a versatile synthetic intermediate of artificial HMG Co-A reductase inhibitors" TETRAHEDRON LETTERS, vol. 34, no. 3, 1993, pages 513-516, XP000886348 page 516	1-10
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Y	WO 97 19917 A (L'OREAL) 5 June 1997 (1997-06-05) claim 47	1-10

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/GB 00/00481

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		EP 0805800 A	12-11-1997
		JP 10504845 T	12-05-1998